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Does left ventricular reverse remodeling influence long-term outcomes in patients with Chagas cardiomyopathy?

Running title: Left ventricular reverse remodeling in Chagas cardiomyopathy

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Abstract

Background: The impact of left ventricular reverse remodeling (LVRR) on the prognosis of Chagas cardiomyopathy is unknown. The aim of this study was to determine whether the presence of LVRR can predict mortality in these patients.

Methods: From January 2000 to December 2010, the medical charts of 159 patients were reviewed. LVRR was defined as an increase of left ventricular ejection fraction (LVEF) and a decrease of left ventricular end-diastolic diameter (LVDD) by two-dimensional echocardiography. No patient underwent cardiac resynchronization therapy or required mechanical ventricular assistance.

Results: At baseline, median (25th–75th) LVDD was 64 mm (59–70), and median LVEF was 33.2% (26.4–40.1). LVRR was detected in 24.5% of patients in a 40-month (26–64) median follow-up. In the LVRR group, LVDD decreased from 64mm (59–68) to 60 mm (56–65; $p < 0.001$), and LVEF increased from 31.3% (24.1–39.0) to 42.5% (32.2–

47.7; $p < 0.001$). However, LVRR was not associated with heart failure hospitalization, cardiogenic shock, heart transplantation, or mortality ($p > 0.05$ for all comparisons). The Cox proportional hazard model analysis identified only cardiogenic shock (hazard ratio [HR]: 2.41; 95% confidence interval [CI]: 1.51–3.85; $p < 0.001$) and serum sodium level (hazard ratio, 0.91; 95% CI: 0.86–0.96; $p < 0.001$) as independent predictors of all-cause mortality.

Conclusions: Left ventricular reverse remodeling occurs in one quarter of patients with Chagas cardiomyopathy and have no impact on the outcome of patients with this condition.

Key words: left ventricular remodeling, heart failure, Chagas cardiomyopathy, prognosis; mortality

Introduction

In the current era, Chagas disease is still a major health problem in Latin America, where about 10 million individuals are carriers of the disease, and about 10,000 people die as result of the disease each year [1]. In view of international immigration, Chagas disease has spread throughout the world, and the global costs associated with this disease are about 7.2 billion United States Dollars (USD) annually, this is higher than that observed in several types of cancer [2].

The disease is caused by *Trypanosoma cruzi*, a protozoan transmitted to humans through the feces of a sucking bug. Infection usually occurs in infancy. Approximately two decades after infection, about 30% of infected patients develop chronic cardiomyopathy and severe complications, as chronic systolic heart failure, and sudden cardiac death [3].

Chronic heart failure (CHF) secondary to Chagas cardiomyopathy (CC), CC has a poor prognosis compared to patients with ischemic cardiomyopathy [4], hypertensive cardiomyopathy [5], or idiopathic dilated cardiomyopathy [6, 7]. The histopathological findings in the chronic stage of CC are focal myocarditis that leads to myocyte loss, reparative, and confluent fibrosis throughout the myocardium, ultimately leading to geometric changes and ventricular systolic dysfunction i.e., ventricular remodeling [8].

Left ventricular reverse remodeling (LVRR) is characterized by a decrease of left ventricular (LV) dimensions, normalization of LV shape and improvement of systolic function [9]. A favorable response to drug therapy with angiotensin converting

enzyme inhibitors, beta-blockers and aldosterone antagonists has been reported, with almost complete reversal of LV dysfunction [10–12]. Although Chagas heart disease has been extensive and intensively studied over the past 20 years, a limited number of studies have assessed cardiac remodeling quantitatively in long-term follow-up in this setting [13, 14]. Male gender and systemic blood pressure seem to be independent predictors of cardiac remodeling [15].

The ability of treatment for heart failure to decrease left chamber size and to improve left ventricular ejection fraction (LVEF) can identify CC patients with a modifiable condition and better long-term prognosis. Accordingly, the aim of this study was to determine whether LVRR could predict all-cause mortality in patients with CC in long-term follow up.

Methods

Patients selection

This single-center study retrospectively evaluated the medical charts of patients with two positive serologic tests for Chagas disease (hemagglutination and indirect immunofluorescence staining) according to the World Health Organization recommendation [16]. The clinical diagnosis of heart failure was made by attending physicians based on Framingham Criteria for the diagnosis of CHF [17]. After the clinical diagnosis of CHF, a two-dimensional (2D) echocardiography was used for each patient to confirm the clinical diagnosis, quantify this condition using LVEF, and to guide treatment. Individuals with the clinical diagnosis of CHF, secondary to CC and LVEF < 55% on first 2D echocardiography confirming LV systolic dysfunction were initially screened for this study. Patients with a concomitant disease that could potentially cause heart disease by itself were excluded.

This study was conducted in accordance with the Declaration of Helsinki and approved through the local Human Research Ethics Committee of São José do Rio Preto Medical School (CAAE — 02716112.6.0000.5415). The need for individual informed consent was waived, as this study was a retrospective analysis of prospectively collected data for routine care, and breach of privacy or anonymity did not occur.

Data availability

The data sets generated and/or analyzed during the current study are not publicly available due to the use of potentially identifying postal codes in the deprivation analysis, as approved by the local Human Research Ethics Committee, but they are available upon reasonable request.

Baseline measurements and 2D echocardiographic conditions

The demographics data, New York Heart Association (NYHA) functional class, heart rate, systemic arterial pressure, medical history, standard laboratory tests, 12-lead resting electrocardiogram and cardiac electronic implantable devices information were obtained upon study entry and retrieved from the medical chart records.

Local specialists in 2D echocardiography did the echocardiographic examination with patients in the left lateral position. Standard parasternal, apical and subcostal views were obtained. Routinely, physicians did place the transducer as far laterally and caudally as possible in the apical windows to maximize LV cavity size and avoid foreshortening during measures. LVEF was measured by the Simpson method in the apical 4-chamber view, which was used for the main analyses, as well as apical 2-chamber view when possible. Wall motion abnormalities analyses, LV end-systolic diameter, left ventricular end-diastolic diameter (LVDD), and right ventricular dimension were measured according to the American Society of Echocardiography recommendations [18].

Although there is lack of standardized definitions for reverse remodeling [19], in the present investigation, LVRR is defined by the simultaneous presence of the following conditions: a) occurrence of an increase of LVEF concomitant with a decrease in LVDD; b) this improvement occurred in the absence of cardiac resynchronization therapy or mechanical ventricular assistance, as also described by Amorim et al. [9]. At the time of the study period, LV volumes were not routinely measured.

Prospective follow-up

The patients were routinely followed from January 02, 2000 to December 30, 2010 at the Cardiomyopathy Outpatient Service, Hospital de Base, São José do Rio Preto Medical School, a public referral center for severe CHF management in the northwest of São Paulo, Brazil. The heart failure medical therapy information was

retrieved from a prospectively collected database of patients. All patients received evidence-based treatment for CHF, according to international guidelines at that time. Thus, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blocks and beta-blockers at targeted or maximal tolerated doses was considered for all patients. Those with pitting edema received furosemide, while those in the NYHA class III/IV with a LVEF < 30% were treated with digoxin. Patients usually visited the outpatient service every 4 months, and a senior heart failure specialist supervised the treatment given. Patients were followed until the study was closed; they were also excluded at heart transplantation or death.

Data analysis

Data were analyzed using the IBM SPSS Statistical Package v.21 (IBM Corporation, Armonk, NY). Variables are presented as absolute numbers and percentages and median and interquartile ranges (25th and 75th percentile) when applicable. Due to the lack of Gaussian distribution, continuous variables were compared using the nonparametric Mann-Whitney test. Chi-square or the Fisher exact test was used to compare categorical variables.

The Cox proportional hazards model was used to evaluate the ability of LVRR to independently predict all-cause mortality during long-term follow-up. In the multivariable model, variables with a p value < 0.10 in the univariate model, and those with known prognostic significance were entered into the backward stepwise approach to establish independent predictors of death. The Spearman test was used to establish a correlation between continuous variables. The variable which correlated with others and with the highest Wald coefficient remained in the model, whereas the other was ruled out. Thus, each variable entered the multivariable model in a proportion of at least 10 events in an attempt to avoid overfitting. The adjusted odds ratio (OR) and 95% confidence intervals (95% CI) were calculated for predictors.

Cumulative survival graphics (Kaplan-Meier) were constructed to demonstrate differences in event-free survival (mortality from all-causes). P values of < 0.05 were considered statistically significant (two-tailed).

Results

Potentially two hundred thirty-four patients were screened for taking part in this investigation. However, a total of 75 individuals (32%) did not undergo another comparative 2D echocardiography during the follow-up because they had died before this. Therefore, they were excluded from this investigation. In this context, the study evaluated 159 patients (64.2% male) who had a median age of 57 (47–66) years, and were followed over a period more than 10 years. The baseline characteristics of the patients are shown in Table 1. These individuals were divided into two groups: with and without LVRR by echocardiographic evaluations. A similarity ($p > 0.05$) for all variables was observed in the present series.

The current study population received maximal tolerated daily doses of medications, considering samples from drug classes with known prognostic impact in ventricular remodeling. LVRR group received mean daily dose (mg/day) of enalapril (15.0 ± 5.8), captopril (106.3 ± 49.6), losartan (44.2 ± 11.0), carvedilol (27.6 ± 21.1), metoprolol succinate (116.7 ± 58.7), spironolactone (33.3 ± 24.3) and non-LVRR group received mean daily dose of enalapril (14.3 ± 8.7 ; $p = 0.357$), captopril (75.8 ± 38.0 ; $p = 0.120$), losartan (50.0 ± 24.2 ; $p = 0.789$), carvedilol (26.3 ± 17.9 ; $p = 0.860$), metoprolol succinate (128.1 ± 63.6 ; $p = 0.585$), spironolactone (27.5 ± 12.4 ; $p = 0.346$), showing no difference between groups for optimized therapy, according to guideline recommendations during the long-term follow-up.

Thirty-nine patients (24.5%) with CC presented LVRR during their follow-up. Comparing the first and the last 2D echocardiography, this group showed a median of 3.0 mm (1 to 6 mm) for absolute reduction of LVDD, representing a median of 5.1% (1.7 to 10%) reduction. For this group, a median of absolute improvement for LVEF of 7.0% (4.0 to 11.6%) was also detected, representing around 23.6% (12.7 to 39.7%) of improvement. There was a significant difference between this group and the group of individuals with LVRR ($p < 0.001$) for all previous measures. Right ventricle diameter and wall motion abnormality did not differ between groups (Table 2).

Standard laboratory tests, 12-lead resting electrocardiographic findings and using cardiac electronic implantable devices observed at study entry were not associated with LVRR occurrence. Moreover, patients with LVRR showed no difference for hospitalization due to acute decompensated heart failure (59.0%), cardiogenic shock (17.9%), and the need to heart transplantation (10.3%) compared to patients without LVRR (65.8%, $p = 0.438$; 29.2%, $p = 0.167$; and 8.3%, $p = 0.747$; respectively).

The Cox proportional hazards model showed a similar situation for late-mortality (over period of more than 10 years) between individuals without LVRR (54.2%) compared to individuals with LVRR (46.2%, $p = 0.384$). After adjustment, six variables were used in the multivariate model: age (years), gender (male), cardiogenic shock, left anterior fascicular block, serum sodium level, and LVRR. Only two variables were retained as independent predictors of long-term mortality: cardiogenic shock (hazard ratio [HR]: 2.41, 95% CI 1.51–3.85; $p < 0.001$) and serum sodium level (HR: 0.91, 95% CI 0.86–0.96; $p < 0.001$; Table 3).

The Kaplan-Meier survival analysis of patients with and without LVRR during follow-up is shown in Figure 1. No difference between either group was observed regarding survival.

Discussion

In this study, LVRR in CC was evaluated as a predictor of long-term mortality. According to available research, this is the first study of a cohort of patients with CHF secondary to CC evaluating the role of LVRR on outcome in an over 10-year follow-up. the present study shows no survival improvement despite of LVRR, thus confirming a dismal prognosis and severity of CHF secondary to CC.

Cardiac reverse remodeling with medical treatment of CHF is well established, with demonstrable decreases in LV diameter and improvement in LV function [20–25]. It should be noted that, although the volumetric measurements seem to provide the most powerful data, LVEF measurements are simpler to obtain and are indeed a marker of the remodeling process. As LV volume increases, there is a tendency for a concomitant and usually parallel decrease in LVEF, which can be used, itself, as a marker of the remodeling process [26]. Interestingly, similar to the results provided by Ramasubbu et al. [27] using the echocardiography database from the ESCAPE trial [28], the current study demonstrated that changes in these parameters were not associated with outcome improvement (long-term mortality) in patients with CC as well. In this context, despite LVRR evidenced by improvement in cardiac chamber size and LV function, factors as persistent neurohormonal activation, increased oxidative stress, and inflammatory/immunological cardiomyocyte damage can be a potential hypothesis to explain the present findings [19, 29].

Only two previous studies which included patients with CC aiming at assessing clinical predictors for long-term cardiac remodeling was previously performed in a similar cohort. In both studies [13, 15], in contrast to the present results, no significant reduction for LVDD was observed during follow-up. It is possible that optimized clinical treatment provided to patients in the current study, including targeted or maximal tolerated doses of angiotensin converting enzyme inhibitors and spironolactone associated to beta-blockers, can account for these discrepant results. Moreover, findings herein are similar to those observed in other populations [30, 31].

The therapeutic agents, mainly angiotensin converting enzyme inhibitors and beta-blockers, modify the remodeling process and frequently add other clinically relevant benefits in reducing morbidity and mortality in cardiomyopathy patients [32]. Several clinical trials using a variety of beta-blockers have demonstrated improvements in symptoms, ventricular function, functional capacity, and survival in patients with CHF due to ischemic and dilated cardiomyopathies [33–35]. Some studies with beta-blockers that included patients with CC showed similar benefits [36–40].

Experimentally, a recent study designed to evaluate the role of carvedilol in the context of Chagas disease concluded that the drug did not attenuate cardiac remodeling or mortality in a model of CC [41]. This contrasts with other experimental studies in which metoprolol was capable in reverting electrocardiographic abnormalities in a rat model of Chagas disease, was probably because the reversal of catecholamine toxicity in this model [42, 43]. In fact, parasympathetic derangement is believed, along with microvascular dysfunction and autoimmunity, to play a central role in the pathogenesis of chronic Chagas heart disease [44]. Thus, in the present study, optimized pharmacological treatment confirmed its association with LVRR, considering the reduction of LVDD and improvement of LVEF, although it has not positively impacted on survival.

Inotropic support and serum sodium level were independent predictors for mortality in the current investigation. These findings probably reflect the severity of the study population in which about a quarter of individuals showed cardiogenic shock during follow-up. Therefore, this may account, at least in part, for the ability of inotropic support to predict hyponatremia in patients with CC and, consequently, ventricular remodeling [45, 46].

Limitations of the study

There are some limitations to the present study. This work is a retrospective analysis of prospectively collected single-center data and thus, carries the inherent disadvantages of retrospective studies. All echocardiographic parameters were not available in all patients, and therefore only parameters that had paired measurements (at baseline and follow-up) were used in the analysis, resulting in a smaller sample size. Unfortunately, LV volumes were not obtained, a finding that could better explain LVRR. It must be emphasized that 32% of patients were excluded from the study because they had died before undergoing comparative echocardiography. This reflects the mortality associated with Chagas disease patients in the real world. Intra- and interobserver variability for the echocardiography lab was not mentioned; therefore, it was difficult to determine whether the mean changes in parameters fell within the measurement variability or reflected true changes. Additionally, multivariate analysis included only those factors available in the documented database. Some factors that have an effect on prognosis might not have been examined. Thus, present results may not be applicable to other specific patient cohorts without further study into the various subgroups. Despite these caveats, it should be emphasized that this study was performed in a cohort followed at a tertiary referral center for heart failure treatment, where patients received the best therapy possible. In addition, the data obtained allowed us to perform an ample statistical analysis, which provided its great reliability. Finally, the investigation reflects the relentless prognosis of CC in the real world, independent of LVRR.

Conclusions

The present study suggests that LVRR does not predict a reduction in long-term all-cause mortality in patients with CC. This is the first study to show that the severity of disease progression seems to dissipate the potential benefit of LVRR in patients with CC. Further research, however, with larger sample sizes, should be conducted to confirm these findings.

Conflict of interest: None declared

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Table 1. Baseline characteristics of 159 patients analyzed for occurrence of left ventricular reverse remodeling (LVRR).

Baseline characteristics	All patients (n = 159)	LVRR+ (n = 39)	LVRR– (n = 120)	P
Variable				
Age [years]	57 (47–66)	58 (52–67)	56 (45–65)	0.159
Gender (male)	102 (64.2)	23 (59.0)	79 (65.8)	0.438
NYHA classes I and II	118 (74.2)	33 (84.6)	85 (70.8)	0.087
NYHA classes III and IV	41 (25.8)	6 (15.4)	35 (29.2)	0.087
Heart rate [beats/min]	68 (60–78)	68 (60–80)	68 (60–76)	0.681

SBP [mmHg]	110 (100–120)	110 (100–120)	110 (100–120)	0.687
DBP [mmHg]	70 (60–80)	70 (70–80)	70 (60–80)	0.136
Diabetes mellitus	4 (2.5)	2 (5.1)	2 (1.7)	0.252
Laboratory analysis:				
Hemoglobin [g/dL]	13.2 (12.0–14.0)	13.8 (12.0–14.1)	13.2 (12.0–14.0)	0.877
Sodium [mg/dL]	141 (138–144)	141 (137–144)	141 (138–144)	0.794
Potassium [mg/dL]	4.4 (4.1–4.8)	4.4 (3.9–4.8)	4.4 (4.1–4.8)	0.869
Creatinine [mg/dL]	1.2 (1.0–1.4)	1.1 (1.0–1.3)	1.2 (1.0–1.4)	0.157
CKD-EPI [mL/min/1.73 m ²]	63.5 (51.1–78.6)	65.3 (52.2–78.6)	63.3 (50.6–79.2)	0.658
Electrocardiography				
Atrial fibrillation	41 (25.8)	12 (30.8)	29 (24.2)	0.413
ICD	23 (14.5)	6 (15.4)	17 (14.2)	0.851
Pacemaker	84 (52.8)	18 (46.2)	66 (55.0)	0.336
LBBB	21 (13.2)	3 (7.7)	18 (15.0)	0.242
RBBB	63 (39.6)	16 (41.0)	47 (39.2)	0.837
LAFB	59 (37.1)	15 (38.5)	44 (36.7)	0.840
Low voltage of QRS	9 (5.7)	1 (2.6)	8 (6.7)	0.455
VPC	71 (44.7)	19 (48.7)	52 (43.3)	0.557

Data are shown as median (25th–75th) or number (%). N — number of individuals; NYHA — New York Heart Association functional class; SBP — systolic blood pressure; DBP — diastolic blood pressure; CKD-EPI — estimated glomerular filtration rate according Chronic Kidney Disease Epidemiology Collaboration; ICD — implantable cardioverter-defibrillator; LBBB — left bundle branch block; RBBB — right bundle branch block; LAFB — left anterior fascicular block; VPC — ventricular premature contraction

Table 2. Comparison between first and last two-dimensional-echocardiography (2D-ECHO) during follow-up.

Baseline characteristics	All patients (n = 159)	LVRR+ (n = 39)	LVRR– (n = 120)	P
First 2D-ECHO:				
LVDD [mm]	64 (59–70)	64 (59–68)	64 (59–71)	0.605
LVSD [mm]	54 (49–60)	56 (50–60)	54 (48–60)	0.440
RVD [mm]	23 (19–28)	24 (20–29)	23 (18–28)	0.272
WMA	54 (34.0)	12 (30.8)	42 (35.0)	0.628
LVEF [%]	33.2 (26.4–40.1)	31.3 (24.1 – 39.0)	33.5 (27.0–40.8)	0.223
Last 2D-ECHO:				
LVDD [mm]	65 (60–72)	60 (56–65)	67 (62–74)	< 0.001
LVSD [mm]	56 (49–63)	49 (42–55)	58 (52–64)	< 0.001
RVD [mm]	25 (20–33)	27 (22–35)	25 (19–32)	0.485
WMA	50 (31.4)	11 (28.2)	39 (32.5)	0.616
LVEF [%]	31.7 (24.8–41.8)	42.2 (32.2–47.7)	30.0 (22.7–36.7)	< 0.001
Comparison				
LVDD:				
Absolute difference [mm]	1.0 (–1.0 to 4.0)	–3.0 (–6.0 to –1.0)	2.0 (0.0 to 5.0)	< 0.001
Relative difference [%]	1.4 (–1.8 to 6.0)	–5.1 (–10.0 to –1.7)	3.2 (0.0 to 8.1)	< 0.001
Comparison				
LVEF:				
Absolute difference [mm]	0 (–7.8 to 6.4)	7.0 (4.0 to 11.6)	–3.1 (–10.6 to 3.2)	< 0.001
Relative difference [mm]	0 (–23.3 to 23.6)	23.6 (12.7 to 39.7)	–8.4 (–28.8 to 12.0)	< 0.001

Data are shown as median (25th–75th) or number (%). LVRR — left ventricular reverse remodeling; N — number of individuals; LVDD — left ventricular end-diastolic

diameter; LVSD — left ventricular systolic diameter; RVD — right ventricular diameter; WMA — wall motion abnormalities; LVEF — left ventricular ejection fraction

Table 3. Cox proportional hazard model for independent predictors of long-term mortality.

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
All patients						
Age [years]	1.00	0.98–1.01	0.688			
Gender (male)	1.43	0.89–2.30	0.142			
LVR status	0.76	0.45–1.28	0.303			
Cardiogenic shock	2.49	1.58–3.91	< 0.001	2.41	1.51–3.85	< 0.001
Left anterior fascicular block	1.72	1.12–2.65	0.014			
Serum sodium level	0.91	0.86–0.96	0.001	0.91	0.86–0.96	< 0.001

HR — hazard ratio; CI — confidence interval; LVR — left ventricular reverse remodeling

Figure 1. Kaplan-Meier survival analysis of patients with and without left ventricular reverse remodeling considering reduction of left ventricular end-diastolic diameter and improvement of left ventricular ejection fraction.

